See related article on pg 2086

The Thinning Top: Why Old People Have Less Hair

Sashank K. Reddy[1,2] and Luis A. Garza[1]

Changes in the hair cycle underlie age-related alopecia, but the causative mechanisms have remained unclear. Chen *et al.* point to an imbalance between stem cell–activating and –inhibitory signals as the key determinant of age-related regenerative decline. Further, they identify a secreted protein, follistatin, that may be able to shift the balance toward renewal.

Journal of Investigative Dermatology (2014) **134,** 2068–2069. doi:10.1038/jid.2014.172

An intriguing puzzle in the field of regeneration is why regenerative capacity declines with age. Younger animals have a greater ability to recover from damage and to adjust to physiologic tissue loss than do older ones. In humans, for example, young children can regenerate missing calvarial bone, whereas adults fail to do so (Drake *et al.*, 1993). In rodents, peripheral nerve regeneration is more robust in younger animals than in older ones (Kang and Lichtman, 2013). Similarly, in the skin the rate of both epidermal renewal and hair follicle cycling declines with age (Keyes *et al.*, 2013). The reasons for age-related loss of regenerative ability are largely unknown. Chen *et al.* (2014) use clever transplantation experiments to characterize changes in hair cycling with age and to provide molecular mechanisms for age-related decline.

Earlier experiments by Chase in the 1950s demonstrated that hair regeneration in mice proceeds in waves of hair growth emanating from central foci (Chase, 1954). In the current study, Chen *et al.* (2014) reexamined this phenomenon by clipping pigmented mouse hairs and observing patterns of hair reemergence with time. By comparing mice at varying ages, from 12 to 26 months, they observed that domains of hair growth shrink with increased age, reflecting a decrease in both the rate of hair wave propagation and the distance a wave will ultimately travel. Further, in mice older than 12 months of age, they noted an increase in the duration of telogen—the resting phase of the hair cycle—which they termed telogen retention.

Hair follicles are regenerated throughout an organism's lifetime via mobilization of long-lived stem cells in the bulge region. At anagen—the growth phase of the hair cycle—these cells divide to self-renew and to give rise to hair germ cells, which then reconstitute mature follicles (Alonso and Fuchs, 2006). Given this, one could envision at least two explanations for the observed decrease in follicle regeneration with age: (1) stem cells that repopulate hair follicles decrease in number, and/or (2) stem cell activation is decreased as animals age. Evidence from human studies argues against a decrease in stem cell number, as bulge stem cells are maintained in scalp skin from patients with age-related alopecia (Garza *et al.*, 2011). Consistent with this, the authors find that both young and old mice have similar numbers of stem cells in the bulge as assessed by immunofluorescence for stem cell markers and by FACS. To determine whether reduced regeneration reflects decreased stem cell activation, the authors grafted patches of skin from older animals in telogen onto the backs of young immunodeficient mice. Strikingly, when the experiments were performed with small patches of donor skin, telogen retention was fully reversed, leading to anagen onset and hair follicle regeneration throughout the donor skin. The ensuing wave of hair regeneration even extended into the surrounding skin of the recipients. Importantly, hair follicle cycling in grafted skin persisted through multiple cycles, indicating a true reversal of the telogen retention phenotype, rather than a transient stimulation of folliculogenesis by surgical trauma. Larger skin grafts did not respond as completely, however. Although initiation of hair cycling was observed at the periphery of larger grafts, the central portions remained in telogen from the second grafted cycle onward. In both small and large skin grafts, waves of follicle generation were initiated at the boundary between donor old skin and recipient younger skin. This suggests that factors elaborated by recipient skin activate previously refractory follicles in the donors.

To characterize mechanisms governing the differing regenerative capacities in young and old mice, the authors examined factors previously known to regulate anagen onset. Activation of the canonical Wnt pathway has been demonstrated to precede anagen in mice (Myung *et al.*, 2013). The authors found that canonical Wnt ligands and the Wnt effector β-catenin were present at similar levels in anagen hair germs of both young and old mice. However, older mice had far higher levels of the Wnt inhibitors Dkk1 and Sfrp4. Similarly, BMP2, which this group had previously identified as a negative regulator of anagen onset, was upregulated in older mice (Plikus *et al.*, 2008). These data suggest that the balance between stem cell–activating and –inhibitory signals is shifted toward inhibition in older mice. To identify factors that may shift this balance, the authors focused on follistatin, a known positive regulator

[1]*Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA and* [2]*Department of Plastic Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA*

Correspondence: Luis A. Garza, Department of Dermatology, Johns Hopkins University School of Medicine, CRB II Suite 204, 1551 Orleans Street, Baltimore, Maryland 21231, USA.
E-mail: LAG@jhmi.edu

Clinical Implications

- Hair follicles in younger mice cycle more frequently compared with those in older mice.
- Factors extrinsic to hair follicles can reactivate hair cycling in dormant older skin.
- The secreted protein follistatin enhances hair follicle cycling, pointing to a potential therapeutic strategy for alopecia.

of anagen onset (McDowall *et al.*, 2008). Follistatin gene expression was higher in the skin of younger mice. Further, follistatin levels were increased in older skin grafts following transplantation onto younger mice. As follistatin is a secreted molecule, it may be responsible for the reactivation of hair cycling in telogenic donor skin when grafted onto younger recipients. Strikingly, follistatin-releasing beads were sufficient to convert hair follicles in telogen into anagen when placed on the skin of young mice. Whether this effect can be recapitulated in older mice in telogen retention remains to be seen.

These results support an emerging understanding that aging in skin is not fully a cell autonomous phenomenon. However, as intriguing as these findings are, they raise several new questions. The mechanisms by which follistatin or other extrafollicular signals activate stem cells in the hair bulge are unknown. As follistatin is a known BMP antagonist (McDowall *et al.*, 2008), and as younger mice express higher levels of follistatin, it is tempting to speculate that younger mice are less sensitive to the anagen-inhibitory effects of BMP2. In addition, whether follistatin is the only molecule in young skin capable of rejuvenating older follicles is not clear. Finally, the reason why waves of hair regeneration dissipate in the center of larger skin grafts remains uncertain. It will be interesting to determine whether this reflects intrinsic hair follicle defects or deficiencies in extrinsic signals. These questions aside, the present study is a compelling demonstration that extrafollicular stimuli govern differences in hair renewal capacities in young and old mice. At least when it comes to hair cycling, you really are as young as your neighbors.

CONFLICT OF INTEREST
The authors state no conflict of interest.

ACKNOWLEDGMENTS
LAG was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, part of the National Institutes of Health, under Award Number R01AR064297.

REFERENCES

Alonso L, Fuchs E (2006) The hair cycle. *J Cell Sci* 119:391–3

Chase HB (1954) Growth of the hair. *Physiol Rev* 34:113–26

Chen CC, Murray PJ, Jiang TX *et al.* (2014) Regenerative hair waves in aging mice and extra-follicular modulators follistatin, Dkk1 and Sfrp4. *J Invest Dermatol* 134: 2086–96

Drake DB, Persing JA, Berman DE *et al.* (1993) Calvarial deformity regeneration following subtotal craniectomy for craniosynostosis: a case report and theoretical implications. *J Craniofac Surg* 4:85–9

Garza LA, Yang CC, Zhao T *et al.* (2011) Bald scalp in men with androgenetic alopecia retains hair follicle stem cells but lacks CD200-rich and CD34-positive hair follicle progenitor cells. *J Clin Invest* 121:613–22

Kang H, Lichtman JW (2013) Motor axon regeneration and muscle reinnervation in young adult and aged animals. *J Neurosci* 33: 19480–91

Keyes BE, Segal JP, Heller E *et al.* (2013) Nfatc1 orchestrates aging in hair follicle stem cells. *Proc Natl Acad Sci USA* 110:E4950–9

McDowall M, Edwards NM, Jahoda CA *et al.* (2008) The role of activins and follistatins in skin and hair follicle development and function. *Cytokine Growth Factor Rev* 19:415–26

Myung PS, Takeo M, Ito M *et al.* (2013) Epithelial Wnt ligand secretion is required for adult hair follicle growth and regeneration. *J Invest Dermatol* 133:31–41

Plikus MV, Mayer JA, de la Cruz D *et al.* (2008) Cyclic dermal BMP signalling regulates stem cell activation during hair regeneration. *Nature* 451:340–4

See related article on pg 2114

Toxic Interaction between Th2 Cytokines and *Staphylococcus aureus* in Atopic Dermatitis

Jeffrey B. Travers[1,2]

Patients with atopic dermatitis (AD) are commonly colonized/infected with *Staphylococcus aureus*, and this bacterium is known to worsen the dermatitis. In this issue, Brauweiler *et al.* demonstrate a newly discovered mechanism by which Th2 cytokines involved in AD augment the toxicity of the lytic staphylococcal protein alpha toxin. This review presents mechanisms by which Th2 cytokines may interact with *S. aureus* to the detriment of the dermatitis.

Journal of Investigative Dermatology (2014) **134,** 2069–2071. doi:10.1038/jid.2014.122

The vast majority (~90%) of individuals with active atopic dermatitis (AD) are colonized/infected with *Staphylococcus aureus*, a species implicated in worsening the skin disease. The propensity of these patients to harbor staphylococcal bacteria is thought to be due in part to the inhibitory effects of Th2 cytokines (IL-4, IL-13) on antimicrobial peptide production. Through this mechanism

[1]*Richard L. Roudebush VA Medical Center, Indianapolis, Indiana, USA and* [2]*Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, Indiana, USA*

Correspondence: Jeffrey B. Travers, Departments of Dermatology, Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA. E-mail: jtravers@iupui.edu